SIMULATION OF TRANSDERMAL DRUG DELIVERY SYSTEM FOR BREAST CANCER THERAPY USING COMSOL

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ABSTRACT

The objective of this paper is to study the effectiveness if the new method of breast cancer therapy, which is the application transdermal patch for the drug delivery system through the largest organ of human body, the skin. This study was done by simulating the process of drug diffusion using multiphysics software, COMSOL. For this study, we are using two types of drugs which have different physical and chemical properties as the subject, which is Paclitaxel and Doxorubicin. The simulation are done by obtaining the information such as the molecular weight and specific diffusivity of drugs through breast tissue until it reaches the targeted cancerous area. The simulation is computed using multiphysics software- COMSOL, to see how fast the drugs will be delivered to the targeted cancer cell. The effectiveness of this method of therapy by is studied by manipulating the properties of the type of drugs, the diffusivity of the drugs and the volume of the breast modeling. All of these parameters are manipulated by designing mathematical models governed by Fick's Law of diffusion. The differences of the concentration of drug on specific depth of breast tissue are shown by a color spectrum after the simulation was done. The application of transdermal patch in breast cancer therapy is the new type of drugs delivery system which lately has been the subjects of numerous researches, as it has been proven to be more advantageous than normal chemotherapy. The dosage of drug needs to be taken by the patients can be reduced significantly as this system is more topical and it is very specific, as the drugs applied to the skin will be absorbed and straightly attack the targeted cancer cell. Compared to normal chemotherapy, the drug pathway does not go through the vascular system or bloodstream, and it can reduce the side effects brought about by the strong drugs to the body of the patients. By doing this study, further development of this new type of breast cancer therapy can be done, so it can be creates more understanding and optimized as the primary type of breast cancer therapy.

ABSTRAK

Objektif utama kajian ini adalah untuk mengkaji keberkesanan cara terapi baru untuk pesakit barah payudara, iaitu dengan menggunakan pelekat transderma sebagai ejen penghantaran dadah melalui organ terbesar pada tubuh manusia, iaitu kulit. Kajian ini dijalankan dengan mensimulasikan proses resapan dadah dengan mengunakan perisian multi fizik, iaitu COMSOL. Kajian ini akan bertumpu kepada dua jenis dadah yang digunakan untuk terapi barah payudara, dengan sifiat kimia dan fizikal yang berbeza antara satu sama lain, iaitu Doxorubicin dan Paclitaxel. Bagi menjalankan simulasi ini, sifat fizikal yang penting untuk dadah tersebut, iaitu jisim molekular relatif dan juga kadar resapan dadah melalui tisu payudara ke kawasan kanser diperolehi dari dari kajian terdahulu. Simulasi yang dijalankan menggunakan perisian COMSOL ini adalah untuk mengkaji masa yang diambil oleh sesuatu dadah untuk tiba ke kawasan sel kanser. Kadar keberkesanan cara terapi ini dikaji dengan memanipulasikan ciri-ciri seprti jenis dadah yang digunakan, kadar resapan dadah serta isipadu model payudara. Ciri-ciri ini akan dimanipulasikan dengan merekabentuk model matematik berdasarkan *Fick's Law of Diffusion.* Kadar kepekatan dadah yang terdapat pada kedalaman spesifik didalam tisu payudara pada satu-satu masa akan diwakili oleh spektrum warna yang berbeza setelah melalui simulasi ini. Penggunaan pelekat transderma sebagai satu medium penghantaran dadah yang baru untuk terapi barah payudara akhir-akhir ini telah menjadi topik utama dalam kajian-kajian saintifik, kerana keupayaan dan keberkesanannya berbanding rawatan kemoterapi biasa. Dos ubat yang perlu diambil oleh pesakit-pesakit barah dapat dikurangkan, kerana sistem ini lebih bertumpu kepada kawasan kanser dan amat spesifik, kerana dadah yang dihantar menerusi kulit akan terus menuju ke kawasan yang telah dikenalpasti. Berbanding dengan rawatan kemoterapi, dadah itu tidak akan melalaui sistem vaskular mahupun sistem peredaran darah, dan akan mengurangkan kesan sampingan dadah tersebut kepada tubuh pesakit. Diharap dengan kajian ini, kajian bekenaan tentang sistem rawatan baru ini dapat diteruskan, agar ia lebih difahami dan dapat dioptimumkan keberkesanannya di masa akan datang.

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LIST OF SYMBOLS/ABBREVIATIONS

C	Concentration
cm	Centimetre
D	Diffusion constant (specific diffusivity)
Da	Dalton
d	Delta
g	Gram
h	height
mm	Millimetre
mol	Mole
r	Radius
s	Second
t	Time
µm	Micrometer
z	Z-axis
π	Pi
%	Percentage
>	More than/ followed by
AIs	Aromatase inhibitors
ALND	Axillary lymph node dissection
ER	Estrogen receptor
ER+	Estrogen receptor positive
IBIS	International Breast Cancer Intervention Study
PgR+	Progesteron receptor positive
SERMs	Selective estrogen receptor modulators
SLND	Sentinel lymph node dissection
USFDA	United States Food and Drugs Administration

CHAPTER 1

INTRODUCTION

This chapter will provide the brief overview of breast cancer, the conventional therapy of breast cancer, and also the application of transdermal patch as the method of breast cancer therapy. This chapter will also go through the background of the study, the statement of problem for this research, objectives that want to be achieved from this study, the scope of study and also the rational and significances of this study to the scientific and commercial development.

1.1 Background of study

Breast cancer is one of the leading causes of death among women in the world. From the research done by The National Cancer Institute of United States of America, by the age of 50 years old, 1 out of 5 women will develop breast cancer. In Malaysia, the number of women affected by this disease increases from time to time. Although this disease is very dangerous, it is actually a highly treatable if it is detected in the early stage of the cancer.

There are numerous ways that has been developed in order to treat the breast cancer patients, and some of the treatment are surgical treatment, therapy of very strong drugs, or is known as chemotherapy, and also hormonal therapy. The most drastic treatment for breast cancer is through mastectomy, or breast surgery. This approach is considered as the most efficient as it directly discard the tumor, but risk of the cancer to

return is still present and the procedure could leave physical trauma and effect to the patient.

The most widely used method of therapy for breast cancer is using strong drug or chemotherapy. Traditionally, this method is done either by using shot injection, or by using oral drugs. The newest development in chemotherapy is application of transdermal patch, which is an adhesive patch containing the drugs that are applied to the skin, near the targeted breast cancer cell. The drugs will be absorbed by the skin, through the layers of breast tissue, until it reaches the specific region where the cancer cells lies. This study will simulate the effectiveness of different type of drugs used on the transdermal patch to the breast cancer by analyzing its concentration on different depth of breast for a specific time.

1.2 Problem Statement

The efficiency of the used of transdermal patch on the skin for breast cancer treatment rely upon the diffusivity of the drugs through layer of breast tissue, and also the chemical and physical properties of the drugs. The transportation of drugs through the skin is more effective than when it is taken orally or through injection, as the action is more topical and site specific. This study will focus on the use of two different types of drugs, which are Doxorubicin and Paclitaxel. These two drugs have different molecular weight and standard diffusivity, and this study will simulate the diffusion of these drugs in order to analyze its effectiveness. The drug diffusivity factors will also be examined in the simulation, where the drugs diffusivity will be manipulated to obtain the most effective drug diffusivity. Furthermore, the relationship between the breast volume and the efficiency of the treatment is studied. In order to analyze the effectiveness of the drug diffusion, we will simulates the diffusion process using, a multiphysics software, called COMSOL.

1.3 Research Objectives

The main aim of this study is investigating the effectiveness of different type of drugs used on the transdermal patch to the targeted cancer cell. We also want to see how different type parameter affected this type of treatment. This can be achieved by fulfilling these objectives:

1. To compare the effect of diffusivity of different type of drug used on the transdermal patch to the targeted cancer cell.
2. To investigate the effect of the specific drug diffusivity to the efficiency of transdermal drug delivery system.
3. To investigate the relationship between the breast volume and the concentration of drugs on the tissue

1.4 Scope of Studies

This study will focus on the effect of the diffusivity of two different kinds of drugs- Doxorubicin and Paclitaxel- and their efficiency on the treatment of breast cancer. The other parameter that we want to investigate in this study is the effectiveness of the usage of transdermal patch analyzing the specific diffusivity of the drugs used, in order to obtain the most efficient drugs diffusivity. The different breast model with different volume will also be designed in order to obtain the relationship between the breast volume and the efficiency of the treatment. To start this study, we will first obtain the data of the respective drugs, which are the specific diffusivity and the molecular weight of the drugs. The size of the breast will also be calculated to determine the placement of the patch on the breast and also to determine the volume of the breast. When all of this data was obtained, the mathematical model of the simulation will be constructed, and the simulation was run using multi-physics software- COMSOL. By using this software, the graph of the concentration of drugs through the breast on specific time will be obtained and analyzed.

1.5 Rational and Significance of Studies

The rational of this study is provide additional insight to the treatment of breast cancer using transdermal patch as it is still considered a new development in healthcare. This method has been proven to be advantageous, comparing to the traditional chemotherapy method. This technology has been proven safer to the body because it did not affect the other tissue of the body aside from the targeted cancer cell, compared to oral drugs or shot injection, as it diffuse through the skin and did not go through the vascular system. The better understanding of transdermal patch can optimize the concentration of the drugs used and the efficiency of the patch itself. This optimization can decrease the dosage of drugs for cancer treatment, thus reducing the cost of the treatment and making it more affordable.

CHAPTER 2

LITERATURE REVIEW

This chapter will cover about the overview of the statistics of the global and local breast cancer cases, the conventional treatment of breast cancer which includes physical surgery, the chemotherapy using strong drugs and hormonal therapy, and also the general principal of the application of transdermal patch for breast cancer therapy.

2.1 Overview of Breast Cancer Cases

Cancer has become one of most prominent cause of death to globally, especially in the developed nation. The main reason on why cancer continues to develop such a dangerous reputation as the big killer is because of the aging and growth of the world population alongside an increasing adoption of cancer-causing behaviors, particularly smoking, in economically developing countries.

Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008; of these, 56% of the cases and 64% of the deaths occurred in the economically developing world. Based on these data, it was also found that the leading cancer that affects women in the world is breast cancer.

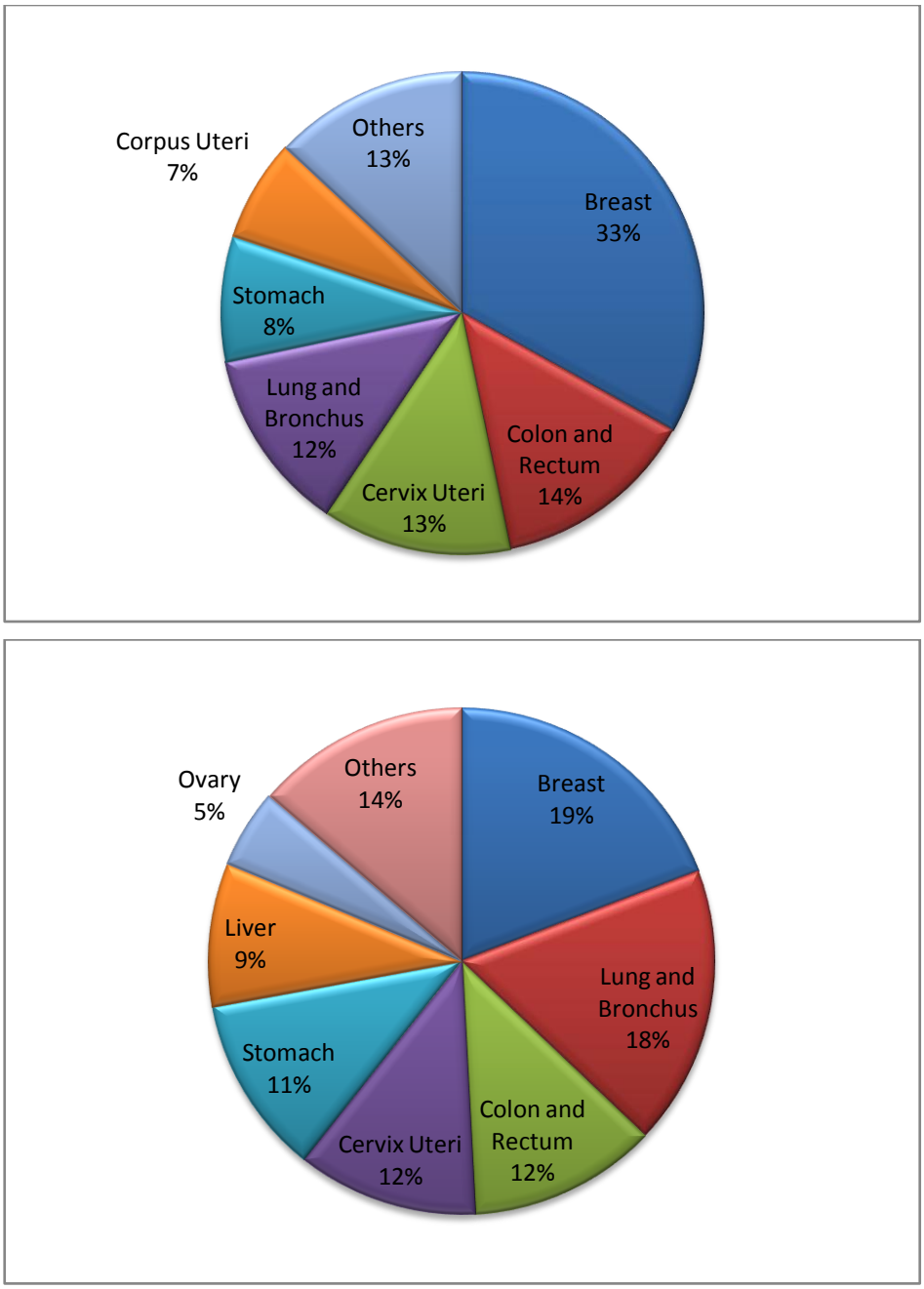

Figure 2.1: Distribution of cancer among women globally (top) and locally (bottom)

Source: National Cancer Registry (2008)

Nearly 70,000 new cancer cases were diagnosed among Malaysians in Peninsular Malaysia between 2003 and 2005, according to a report released in early

2008 on the incidence of the disease in West Malaysia. The Cancer Incidence in Peninsular Malaysia 2003-2005 report, published by the National Cancer Registry (NCR), states that the total 67,792 new cases were diagnosed among 29,596 males (43.7 per cent) and 38,196 females (56.3 per cent). The annual crude rate for males was 100.2 per cent per 100,000 population, and 132.1 per cent per 100,000 for females. The most frequent cancer Malaysians was breast cancer (18 per cent) followed by large bowel cancer (11.9 per cent) and lung cancer (7.4 per cent).

There were 3825 cases reported and 1707 death from breast cancer in Malaysia (Globocan, 2000). They estimated that among 100,000 populations, the crude rate of breast cancer in Malaysia is 34.9 with Age Standardised rate of 41.9 per 100,000. From 2003-2005, breast cancer formed 31.1% of newly diagnosed cancer cases in women, up 1.1% from 2002.

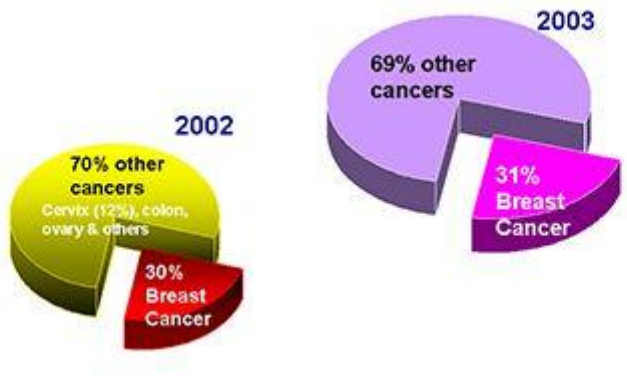

Figure 2.2: Percentage of breast cancer in Malaysia 2002-2003

Source: College of Radiology Breast Health Information Centre (2008)

Breast cancer is not a topical disease that can only affect certain population, the fact that it can kill anyone is very worrying. The National Cancer Institute of America estimated that by the age of 50, one out of 50 women is affected by breast cancer. This number will rise to ten when they reach 80 years old. Over the years from 1993 to 2003, there were a total of 1818 breast cancer patients in the University Hospital. The number of breast cancer patients increased annually, with the highest recorded in 2003. This was 6 times the number of breast cancer patients in 1993.

2.2 Conventional breast cancer treatment

The development in breast cancer treatment has brought about several ways in order to treat this disease. Some of the method that has been used to treat breast cancer is through breast surgery, chemotherapy of strong drugs, and also hormonal therapy.

2.2.1 Breast surgery

Surgery treatment for breast cancer can be divided into two - mastectomy and breast conserving surgery. Mastectomy is the method where the breast structure will be removed in order to remove the cancer cells. For breast conserving technology, it requires more advanced technology, where the cancer cell will be removed using sentinel node biopsy, complimented with radiation. This method allowed women with different form of breast cancer to conserve their breast (Apantaku, 2002).

Study shows that survival rate after breast conserving technology complimented with radiation are equal to the survival rate after mastectomy for stage 1 and 2 breast cancer (Winchester, 1998). Although both method of surgery has been proven to be reliable for cancer patients, mastectomy remains the most common treatment for women with invasive tumor or treatment for early stage of cancer (Morrow et. al., 2001).

The type of surgery that is suitable for the patient depends on the size of the cancer in the breast, whether it has spread to any other part of the body, the size of the breasts and personal wish (CancerHelp UK). According to Opatt et. al., due to lack of knowledge about the option, the patients are not aware with the choices that they have, and still choosing the widely known mastectomy technique, although there are better choices for them.

From the research done by International Breast Cancer Intervention Study (IBIS) in 2002, the women who are eligible for breast cancer surgery are those with high risk benign lesion, which are:

1. Lobular Neoplasia (lobular carcinoma in-situ)
2. Ductal hiperplasia/ atypical lobular hiperplasia
3. Multiple papillomatosis
4. Some type of proliferative fibrocystic mastophaty
5. Primary breast phylloide tumor and relapses.

Recommended surgical care for invasive breast cancer includes removal of the primary tumor and a level I and II axillary lymph node dissection (ALND). The status of the axillary nodes helps to determine the prognosis and guide treatment decisions. Unfortunately, side effects after ALND are relatively common. Some of the effects of ALND are:

- Upper-extremity
- Lymphedema (6%-49%),
- Arm numbness/tingling (7%-75%)
- Pain (16%-56%),
- Impaired shoulder mobility (4%-45%),
- Arm weakness (19%-35%),
- Infections in the breast, chest, or arm (8%).

(Kakuda *et al*,1999 and Petrek *et al*, 2001)

The side effects of axillary lymph node dissection can range from mild to severe and can be a chronic condition that affects patients' quality of life for years after cancer surgery (Maunsell *et al*, 1993).

Recently, a less invasive procedure, sentinel lymph node dissection (SLND), has been developed to stage the axilla for invasive breast cancer. This technique is performed by using a blue dye and a radioactive tracer injected into the breast tissue. SLNs are removed during the surgical procedure, and the pathology results from these nodes have been found to be highly predictive of metastatic involvement in the axilla (Albertini *et al*, 1996). As a result, SLND has become an acceptable alternative to ALND for patients with clinically negative lymph nodes.

Treatment of cancer using surgery can cause physical alteration and emotional trauma to the patients. Most of the patients that undergo mastectomy will need reconstruction for the breast structure. Because surgery is not a safe method, complex and often does not give satisfactory result, it is difficult to accept it as preventive method for breast cancer (Diaz-Faes, 2003).

2.2.2 Chemotherapy

The most common type of breast cancer therapy, chemotherapy, in its simplest sense, is a therapy by ingestion of strong drugs, either orally or through injection, where the drugs will attack the targeted cancer cells and kill it. The main principal of the growth of invasive tumor depends on angiogenesis, which is the formation of blood vessels that will provide the tumor with nourishment and nutrients (Folkman, 1990). Because of this feature, the chemotherapy was designed so that the drugs can pass through the blood vessels to reach the targeted cell and attacking the tumor.

Most popular chemotherapy agents like taxanes and anthracyclines has distinct anti-angiogenic activity (Miller et. al., 2001), while others such as doxorubicin can inhibit collagenase of the cancer cells, preventing it from dividing and stop the growth (Benbow et. al., 1999). Although this method is widely used and has been proven effective, it can cause severe side effects to the patients. The drugs, which were taken orally or through injection, will be distributed to the entire body affecting other rapidly dividing cells, such as hair follicles, nails, mouth and bone marrow as it do not have the ability to distinguish between normal and tumor cells.

Docetaxel and doxorubicin, two widely used drugs for cancer treatment, cause significant drop of blood cell in patients' bone marrow, increasing their risk of getting an infection (Cancer Health UK, 2009). The drop in red blood cell can cause fatigue and breathlessness, while drop in platelets contributes to bruising. Some drugs, like letrozole, caused the depletion of circulating estrogen, causing the patients to experience hot flashes and suffer from bone damage in a long time (Mom et. al., 2006). Letrozole

which were taken by oral capsule is difficult to be administered the right dosage that suitable for the body (Li et. al., 2010)

2.2.2.1 Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel (anhydrous) is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate. Docetaxel (anhydrous) has the following structural formula:

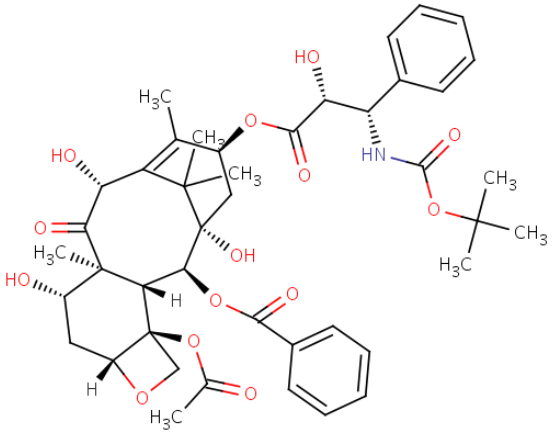

Figure 2.3: Structure of Docetaxel

Source: Drugbank (2005)

Docetaxel kills cells by disrupting the function of microtubules, which are essential for cell survival (Shelley *et al.*,2007). It also inhibits the anti-apoptotic gene Bcl2 and encourages expression of p27, a cell-cycle inhibitor (Van Poppel, 2005), preventing new cells from forming, and causes existing cells to undergo apoptosis and stops other cells from maturing and replicating. As with all cytotoxic agents, the effect of the drug is not specifically aimed at the tumour cells, so 'healthy', normal cells may be affected too, resulting in drug-related side effects.

Docetaxel-containing treatment regimens that is potentially associated with a 20% or greater risk of febrile neutropenia. The incidence of treatment-related mortality associated with docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive docetaxel as a single agent at a dose of 100 mg/m². Baker (1999), has also outline some non-haematological toxicity effect to the patients, such as hypersensitivity reaction, fluid retention, nail toxicity and neuropathy effect.

2.2.2.2 Doxorubicin

Doxorubicin is an anthracycline topoisomerase inhibitor isolated from *Streptomyces peucetius* var. *caesius*. Doxorubicin HCl, which is the established name for (8S,10S)– 10- [(3– amino - 2,3,6– trideoxyαL– lyxo- hexopyranosyl) oxy]– 8- glycolyl- 7,8,9,10- tetrahydro- 6,8,11 trihydroxy- 1- methoxy 5,12- naphthacenedione hydrochloride, has the following structure:

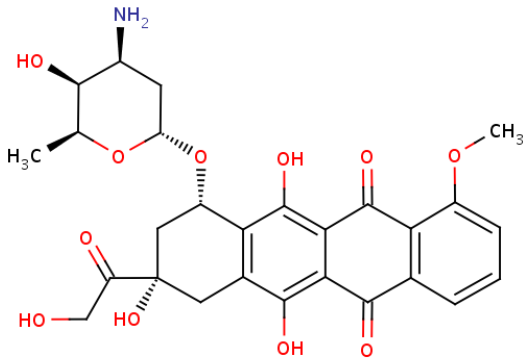

Figure 2.4: Structure of Doxorubicin

Source: Drugbank (2005)

It is a common drugs used in the breast cancer therapy, which work as an anthracycline antibiotic, closely related to the natural product daunomycin, and like all

anthracyclines, it works by intercalating DNA, which inhibits the progression of the enzyme topoisomerase II, that relaxes supercoils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication. The formula is $C_{27}H_{29}NO_{11}$, and the molecular weight is 543.52 g/mol.

The use of doxorubicin may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with doxorubicin.

The acute effects are mainly myelo-suppression, nausea, vomiting, weight loss, arrhythmias and decreased survival, whereas the main chronic effect of doxorubicin is severe cardiomyopathy with precipitant congestive heart failure (Olson *et al*, 2007).

2.2.2.3 Herceptin

Herceptin is a humanized IgGl kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Herceptin is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The important chemical data for herceptin is the chemical formula, which is $C_{6470}H_{10012}N_{1726}O_{2013}S_{42,}$ and the molecular weight is 145531.5 g/mol.

Herceptin administration can result in sub clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving herceptin with anthracycline containing chemotherapy regimens. The treatment of breast cancer using

herceptin can also result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of the treatment with herceptin.

2.2.3 Hormonal therapy

Women hormones, oestrogen and progesterone, can trigger the growth of some cancer cells. Oestrogens exert a large variety of responses in target cells, including promotion of tissue differentiation, morphogenesis, mitogenic activity and development of the mammary gland, which us very beneficial to the general function of human body. However, aside from their essential function in female reproduction, it is also responsible in oncogenesis and maintenance of tumor growth (Ameller *et al*). In fact, oestrogens are regulators of a number of proto-oncogenes coding for nuclear proteins. Oestrogens act on cells via interaction with two types of intracellular receptors. Eventually, the recent discovery of ER has greatly enhanced our understanding of oestrogen action.

The used of hormonal therapy in breast cancer treatment are done in order to lower the level of these hormones and/or block their effect. The goal of the therapy is to develop anti-oestrogens, compounds capable of blocking the effects of estradiol (E2) without displaying any oestrogenic activity on their own.

Hormone therapy can be done either before or after the surgery, or to treat relapses, which is breast cancer that comes back after the surgery (CancerHelp UK). Hormonal therapy is considered as one of the better treatment of cancer as it does match chemotherapy in terms of survival and tumor response. In addition, hormonal therapies produce fewer and less severe adverse effects than chemotherapy (Jordan, 2002)

Patients' response to hormonal therapy depends on their hormone receptor status – estrogen receptor positive (ER+) or progesteron receptor positive (PgR+). Higher response to it brought a greater likelihood to response to the treatment (Osborne et. al., 1980). Approximately 50% to 70% of women benefit from hormonal therapy if their

tumors are positive for both ER and PgR, 33% benefit if their tumors are positive for either type of receptor, and only 11% benefit if their tumors are negative for both types.

There are several therapies that have been developed regarding hormonal therapy for breast cancer, which are including the selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and estrogen receptor (ER) antagonists.

2.2.3.1 Selective Estrogen Receptor Modulators (SERMs)

The first type of hormonal therapy for breast cancer is Selective Estrogen Receptor Modulators (SERMs). The drugs used for this treatment can mimic the action of estrogen in the body, and modulating the estrogen receptor. The most popular drugs that is used in hormonal therapy for breast cancer treatment is Tamoxifen, which is considered the gold standard of the procedure since 1970's. Other drug that has similar function with Tamoxifen is Toremifene.

Some of the adverse effects between Tamoxifen and Toremifene is similar, which are hot flashes, nausea, vomiting and vaginal discharge. Tamoxifen, however, was associated with a higher incidence of thromboembolic events (1.3%- 8.0% vs 0.6%-5.1%), vaginal bleeding (0%-19.8% vs 0.9%-3.7%), and endometrial cancer (0%-1.8% vs 0%) compared with toremifene (Cummings, 2002)

This drug usually recommended to be taken for five years usage, as the used of it longer than five years did not further the benefits, instead it increase dangerous side effects such as blood clots within deep veins (pulmonary embolism), endometrial cancer and stroke.

2.2.3.2 Aromatase Inhibitors (AI)

Aromatase inhibitors stop the production of estrogen in post-menopausal women. Aromatase inhibitors work by blocking the enzyme aromatase, which turns the